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Award Number: W81XWH-11-2-0161

TITLE: Detection of Early lung Cancer Among Military Personnel (DECAMP)

PRINCIPAL INVESTIGATOR: Avrum E. Spira, MD

CONTRACTING ORGANIZATION: Boston University
Boston, MA, 02118

REPORT DATE: October 2013

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2013	Annual	30 September 2012-29 September 2013

4. TITLE AND SUBTITLE

Detection of Early lung Cancer Among Military Personnel (DECAMP)

5a. CONTRACT NUMBER
W81XWH-11-2-0161

5b. GRANT NUMBER
W81XWH-11-2-0161

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Avrum E. Spira, MD
Emily Maple

E-Mail: emaple@bu.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Boston University
Boston, MA, 02118

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The purpose of this work is to develop and validate molecular biomarkers found in blood, other bodily fluids, or tissues, which may be used for the early detection of lung cancer in Military Treatment Facilities and Veteran's Administration Hospitals. Over the course of the second year of this award, we have maintained and appropriately modified the administrative infrastructure needed for two distinct clinical trials. Prototol 1, the validation of non-invasive biomarkers to distinguish cancer from benign lesions among patients with pulmonary nodules, has received full approval to begin recruitment at all 14 clinical sites. We have thus far enrolled ~30 subjects from ten of the clinical sites, and have transferred clinical data imaging and biospecimens from the clinical sites to the coordinating centers. We are currently evaluating the quality of RNA obtained from biospecimens from sites that have recruited at least 3 subjects. We have also modified the inclusion criteria for this protocol based on feedback from the clinical sites. Protocol 2 will recruit a cross-sectional cohort of smokers with early stage lung cancer (n=50) and matched controls (n=30) along with a longitudinal cohort of 800 high-risk smokers in order to develop molecular biomarkers for the preclinical detection of lung cancer. This protocol has obtained regulatory approval at four sites who are currently screening eligible candidates for recruitment purposes. We have appropriately modified our administrative infrastructure to maximize efficiency and clear communication between sites and Boston University. We have also modified biospecimen collection and shipping procedures accordingly, after collecting and reviewing feedback. Based on the above progress, we are strongly positioned to further recruitment into both protocols during the coming year, ultimately helping to develop non-invasive measures for the early detection of lung cancer.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU		19b. TELEPHONE NUMBER *(include area code)*

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Introduction:

The purpose of this work is to develop and validate molecular biomarkers that may be used for the early detection of lung cancer. By recruiting approximately 500 patients with indeterminate pulmonary nodules from Military Treatment Facilities and Veteran's Administration Hospitals, DECAMP plans to identify 75 patients with lung cancer for our molecular studies. For the study to develop tests that can identify the patients at highest risk for having or developing lung cancer, DECAMP will recruit approximately 850 high-risk current and former smokers from these same hospitals, determine whether they have lung cancer now and then follow them annually for up to four years to determine if they develop lung cancer. We expect to identify 50 patients who did not have cancer when they join the study, but develop lung cancer while they are being monitored. The clinical applications of this study will come from the development of tests to more accurately diagnose disease at an early potentially curable stage but also predict the occurrence of lung cancer in the future. Additionally, these biomarkers found in blood, other body fluids, or tissues will be collected more easily and are less invasive than surgery. Non-invasive collection of biological samples will be less painful for the patient and allow easier and more frequent monitoring of disease. The intent of this research is to develop early detection strategies that will ultimately decrease lung cancer deaths. This will improve the health and welfare of the military, and the American public as a whole.

During the second year of this award, we achieved a number of key milestones needed for progression towards the ultimate goals of our consortium. Protocol 1 has been fully approved by local IRBs and HRPO at all 14 military and veteran clinical sites. Before sample collection at clinical sites began, the coordinators provided extensive group and individual formal training, combined with on-going relevant training as needed. Importantly, all sites are actively enrolling subjects into this protocol and collecting relevant biosamples and imaging, closely coordinated by ACRIN and BU.. We have thus far recruited ~30 subjects into this protocol from 10 sites, with clinical data ,imaging and biosamples transferred to the coordinating center . We have begun to perform quality control checks on select biosamples collected including RNA isolation and testing at the Genomic Core at Boston University. We have also formulated and put into action a process for sample transfer and tracking that will allow the Biorepository Core at Boston University to have a working knowledge of physical location of each sample, as well as, tracking its position in testing or storing process. Finally, we have modified the inclusion criteria (nodules size range 7mm-25mm. age>45, pack-yrs >20) for this protocol based on feedback from the clinical sites.

Protocol 2 has been fully approved at three sites, with several sites awaiting local IRB approval, and a number of others awaiting HRPO approval. We have been working closely with the RAs at each site to set up clear and consistent recruiting efforts prior to enrolling our first group of subjects into this trial. . To aid recruitment, we have widely disseminated flyers and informational brochures within the MTF and VA systems.

As a result of protocol recruitment, we have modified areas within the DECAMP infrastructure in an effort to work as effectively and efficiently as possible. Some collection procedures were clarified after RA and PI feedback. Also, several responsibilities have been appropriately reallocated, including, reassigning Ms. Patricia Atkinson to focus specifically on regulatory compliance. Also, the Standard Operating Procedures for both biospecimen and imaging collection have been clarified for clinical site use. A summary of our progress related to each of the tasks in our SOW is more specifically outlined below.

Task 1 Pre-Award Study Development
1a Attended planning meeting hosted by the USAMRMC to present the clinical projects proposed to the four military hospitals and develop the operational features of the Consortium (June 2011)
1b Developed final draft clinical trial protocols for the two proposed studies
1c Developed Case Report Forms (CRFs)
1d Finalized modified budgets in order to provide the necessary resources to the military hospitals

Task 2 Protocol Development (Month 0-6)
2a Received approval for submitted protocols for both clinical projects to Army Surgeon General's Human Research Protection Office (HRPO);
2b Received approval for submitted protocols for both clinical projects to ACR IRB;
2c Submitted and received approval for both protocols at BU IRB,

Task 3 Clinical Trial Development (Month 0-6)
3a Coordinating Center Activities

- Established Steering Committee and initiated calls to review proposed protocol for both clinical projects and recommendations from EABs meeting. There have been several calls completed, October 17, December 13, 2011, February 6, March 28, June 29, 2012, September 25, 2012, January 2013, April 2013, August 2013, and September 2013
- Established Protocol Team which communicates via teleconference bi-weekly.
- Recruited and hired four research associates who will be contract employees at the MTFs
- Developed tracking mechanism between biorepositories and ACRIN DMC

- Administering web user names, passwords, and reader IDs to all appropriate site research personnel
- Developed site readiness tracking tool and continuously updating
- Ordered biomarker collection supplies, preparing biospecimen collection packs for the nodule and screening protocols, in the process of distributing to sites.
- Developed study initiation training conference material
- Conducted site training session via web conference
- Established electronic mail distribution lists and postal directories between the coordinating center and subcontractors and the coordinating center and participating sites
- Established protocol team teleconference schedule (bi-weekly)
- Had first in person meeting with the EAB at Fort Dettrick, MD, on November 2, 2011, to review the proposed study protocols and have amended both protocols based on feedback received from the EAB and DoD.
- Held second EAB meeting via teleconference on April 23, 2012. Discussion based around molecular biomarkers, protocol submission, addition of cross-sectional cohort, questionnaire, and electronic Case Report Forms. We have amended questionnaire and forms based on feedback from EAB
- Held third EAB meting via teleconference on November 6, 2013.
- Established a schedule for teleconference or in-person bi-annual meetings of the EAB and Steering committee
- Executed consortium subcontracts between coordinating center and:
  American College of Radiology, Mitchell Schnall, PI, 1818 Market St, Philadelphia, MA, involves human subject research
  Brown University, Constantine Gatsonis, PI, 121 South Main Street, Providence, RI, involves human subject research
  The University of Texas M.D. Anderson Cancer Center, Ignacio I. Wistuba, PI, 1515 Holcombe Blvd, Unit 176 Houston, TX 77030-4009, involves human subject research
  Regents of the University of California LA, Steve Dubinett, PI, The Regents of the University of California, 11000 Kinross Ave, Ste 102 Los Angeles, CA 90095-1406, involves human subject research
  Middle Tennessee Research Institute (Vanderbilt University), Pierre Massion, PI, 1310 24th Ave S., Rm F-201 Nashville, TN 37212, involves human subject research
- Executed contracts between coordinating center and participating clinical sites:
  Boston VA Research Institute, Inc, R. Goldstein, 150 S. Huntington Avenue Boston, MA 02130, involves human subject research
  Dallas VA Research Corporation, J. Battaile, 4500 South Lancaster Road, Bldg 43, Suite 124, Dallas, TX 75216, involves human subject research
  Denver Research Institute, R. Keith, VAMC-151 1055 Clermont Street Denver, CO 80220, involves human subject research
  Middle Tennessee Research Institute (Vanderbilt University), Pierre Massion, PI, 1310 24th Ave S., Rm F-201 Nashville, TN 37212, involves human subject research
  Trustees of University of Pennsylvania (Philadelphia VA Medical Center), A. Vachani, Philadelphia VA Medical Center, 3900 Woodland Avenue, Philadelphia, PA 19104, involves human subject research
  Regents of the University of California LA (Los Angeles VA Healthcare System), S. Dubinett, West Los Angeles Medical Center, 11301 Wilshire Blvd, Los Angeles, CA 90073, involves human subject research
  Veterans Research Foundation of Pittsburgh, C. Atwood, 7180 Highland Drive, Pittsburgh, PA 15240, involves human subject research

Health Research Inc. Roswell Park Division, M. Reid, Roswell Park, 666 Elm Street, Buffalo, NY, 14263

- Established CRADAS between coordinating center and participating MTFs:
  Naval Medical Center Portsmouth, 620 John Paul Jones Circle, Portsmouth, VA, 23708-2197, involves human subject research
  Naval Medical Center San Diego, Naval Medical Center, 34800 Bob Wilson Drive, San Diego, CA 92134, involves human subject research
  Walter Reed National Military Medical Center, Walter Reed Army Medical Center, 6900 Georgia Ave NW, Washington, DC 20307, involves human subject research
  San Antonio Military Medical Center, Brooke Army Hospital, 3851 Roger Brooke Dr., Fort Sam Houston, TX 78234 and Wilford Hall Medical Center, 2200 Bergquist Drive, Suite 1, Lackland AFB, TX 78236-9908, involves human subject research
- Created DECAMP case reimbursement tracking and reporting program using existing ACRIN case reimbursement program modules
- Completed MTA's between participating sites and biorepositories/pathology lab

3d Site Activities

- Distributed first protocol to each site. Each site has submitted protocol to local IRBs. Full approval (local IRB and DOD): all sites
- Distributed second protocol to all sites. Full approval at: BAMC, Philadelphia VA, and Denver VA;
- Identified staff that will serve as coordinator for DECAMP protocols; submit all information to coordinating center on standardized form to facilitate communication between the coordinating center and participating sites.
- Subawards include the execution of site contracts for fixed infrastructure support and per case reimbursement
- Working with each recruitment site to install TRIAD
- Developed participant recruitment workflow

3f Biostatistics and Data Management Center

- Finalized CRFs.
- Configured ACRIN database for study data collection

3g Imaging Core Lab

- Finalized CRFs associated with image submission
- Completing TRIAD installation at participating sites
- Qualifying participating sites

3i Biospecimen Labs

- Established SOPs and workflow for the biospecimen repository at BU
- Developed tracking system for all samples

Task 4 Clinical Trial Accrual

4a Coordinating Center-General

- Site webinar training completed October 2012
- Monitoring sites as all readiness requirements are satisfied
- Commenced site initiation and training

4b Coordinating Center-Data Management Center

- Baseline forms, program, and follow-up forms activated
- Completed schema for all forms identified above
- Implemented tracking coordination of biospecimen collection activities

4c Coordinating Center-Imaging Core Laboratory
- Confirmed site needs for image transfer, including software and equipment
- Defined imaging parameters: found in Imaging SOPs (DECAMP-1 Completed, DECAMP-2 In progress)
- Finalized QC guidelines per standard ACRIN procedure
- Developed formal imaging management plan
- Received and reviewed test images submitted by sites for image credentialing and qualification

4e Coordinating Center-Biospecimen Core labs
- Obtained required equipment for analysis
- Trained core lab staff on SOPs and workflow
- Provided training for site coordinators

4f Participating Sites
- Approved sites commenced accrual and data collection
- Sites commence accrual and data collection including clinical, imaging, and biospecimens and tissue
- Ongoing data quality checks and imaging quality assurance during period of data submission to the ACRIN data management and imaging core laboratory

4g Biostatistics Cores
- Commenced BC monthly reporting
- Commenced data quality monitoring

Task 5 Clinical Trial Accrual (Month 12-24)
- Monitor in accordance with Monitoring Plan
- Study monitoring occurs on routine CCSC calls
- Case reimbursement administered
- Transfering of biospeciments from sites to biorepository core and other core labs
- Distribution of biospecimens to bioassay labs:
    - Project 1:
        - Airway brushings – Boston University

Key Research Accomplishments:
n/a

Reportable Outcomes:
n/a

Conclusion:
During our second year of this consortium, we have achieved a major milestone by establishing regulatory approval at all clinical sites for Protocol 1, and have enrolled ~30 patients into this protocol from 10 sites. Additionally, Protocol 2 has received ACRIN and HRPO approval, with three clinical sites fully approved to recruit subjects into that protocol. We have established a clinical data, imaging data and biosample workflow and have begun auditing and monitoring of samples and images for Protocol 1 with quality checks for several sites. We have also increased communication efficiency along the channels of regulatory approval between the sites, coordinating center, and DoD. This has allowed us to concentrate efforts on recruitment and planning implementation efforts.